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Assessment of the influence of elevated troponin I levels measured in the perioperative period on the clinical course of patients after heart transplantation in own material

Ocena wpływu zwiększonych stężeń troponiny I mierzonej w okresie okołooperacyjnym na przebieg kliniczny u chorych po transplantacji serca w materiale własnym

Karol Wierzbicki[1], Maciej Bochenek[1], Dorota Sobczyk[1], Irena Milaniak[1], Bogusław Kapelak[1], Dorota Ciołczyk-Wierzbicka[2], Rafał Drwiła[1], Piotr Przybyłowski[1], Krzysztof Bartuś[1], Jerzy Sadowski[1]

[1]Klinika Chirurgii Serca, Naczyń i Transplantologii Uniwersytetu Jagiellońskiego, *Collegium Medicum*, Szpital im. Jana Pawła II w Krakowie
2Katedra Biochemii Lekarskiej Uniwersytetu Jagiellońskiego, *Collegium Medicum* w Krakowie

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Abstract

Introduction: Primary graft failure is a common cause of mortality after heart transplantation (HTX). Troponins are widely used as markers of myocardial ischemia, and they appear to be reliable indicators of multifactorial heart transplant injury.
Aim of the study: The aim of the present study was to assess the relationship between troponin I levels measured over the first days after HTX and the postoperative clinical course, including a 6-month follow-up.
Material and methods: The retrospective analysis included 54 patients (5 females, 49 males), age 12-62 years (median age 52.0, qr. 15.0) after heart transplantation performed according to the same scheme, in whom the postoperative troponin I levels were measured on several consecutive days after HTX. The relationship between Intensive Care Unit (ICU) length of stay, duration of respiratory therapy and troponin levels was assessed in the patients who survived more than 6 months.
Results: There was a positive correlation between the duration of respiratory therapy (median 2.0; qr 1.0) and troponin I levels on several consecutive days after HTX; however, only the relationship on the second postoperative day reached statistical significance. There was also a positive correlation between ICU length of stay (median 7.0, qr 3.0) and troponin I levels. A statistically significant correlation was observed for the troponin I levels on the first, second and third day after HTX. Troponin I levels measured at 0, 2 and 3 days after HTX significantly influenced the survival rate at > 6-month follow-up.
Conclusions: Elevated perioperative troponin levels may significantly influence the clinical course after HTX.
Key words: heart transplantation, troponin I, survival.

Streszczenie

Wstęp: Pierwotna niewydolność przeszczepu jest częstą przyczyną zgonów we wczesnym okresie po przeszczepie serca (ang. *heart transplantation* – HTX). Troponina jako szeroko stosowany marker uszkodzenia mięśnia serca wydaje się dobrym wskaźnikiem wieloczynnikowego uszkodzenia także przeczepionego serca bezpośrednio w okresie okołoperacyjmnym.
Cel pracy: Określenie zależności pomiędzy stężeniami troponiny I mierzonymi w pierwszych dobach po HTX a przebiegiem klinicznym z uwzględnieniem wczesnej i 6-miesięcznej obserwacji chorych w materiale własnym.
Materiał i metody: Badaniem retrospektywnym objęto 54 chorych (5 kobiet, 49 mężczyzn) w wieku 12–62 lat (mediana 52 lata, qr 15,0), u których wykonano przeszczep serca wg identycznego schematu i zmierzono stężenie troponiny I w kolejnych dobach po HTX. Ocenę zależności pomiędzy długością pobytu na Oddziale Intensywnej Terapii (IT) i czasem respiratototerapii a stężeniami troponiny I, przeprowadzono w grupie chorych, którzy przeżyli > 6 mies.
Wyniki: Stwierdzono dodatnią korelację pomiędzy czasem respiratoroterapii (mediana 2,0; qr 1,0) a stężeniami troponiny I w kolejnych dobach po HTX, jednak tylko zależność w 2. dobie była istotna statystycznie.
Stwierdzono także dodatnią korelację pomiędzy czasem pobytu na Oddziale IT (mediana 7,0; qr 3,0) a stężeniami troponiny I. Istotnie statystyczną zależność stwierdzono pomiędzy stężeniami troponiny I ocenianymi w 1., 2. i 3. dobie po HTX. Poziom troponiny mierzony w 0., 2. i 3. dobie po HTX istotnie wpływał na przeżycie chorych > 6 miesiąca.
Wnioski: Podwyższone poziomy troponiny w okresie okołooperacyjnym mogą istotnie wpływać na przebieg kliniczny po HTX.

Adres do korespondencji: lek. Maciej Bochenek, ul. Prądnicka 80, 31-202 Kraków, tel. +48 12 614 30 75, +48 12 614 30 72, fax +48 12 423 39 00, Email: bochenekmd@gmail.com

Słowa kluczowe: przeszczep serca, troponina I, przeżycie.

Introduction

Heart transplantation (HTX) is the ultimate treatment option in patients with end-stage heart failure (if other treatments fail) defined as an accepted treatment in the newest ESC (European Society of Cardiology) guidelines. It improves significantly:

- survival,
- physical capacity,
- quality of life [1].

The newest ESC guidelines maintain the role of heart transplantation for treatment of end-stage heart failure, but its major limiting factor is still the shortage of donor hearts [1].

A half-century has elapsed since the first heart transplantation. Long-term transplant survival has improved significantly. The ISHLT (International Society for Heart and Lung Transplantation www.ishlt.org) Registry shows a half-life time (the time which 50% of patients survived) of more than 10 years, which is better by about half a year than that after the introduction of cyclosporine in the early 1980s [2].

Unfortunately, the number of heart transplants performed each year has not increased and even a reduction has been observed worldwide in recent years. The ISHLT Registry shows that in Europe the number of heart transplants has decreased by over 40% over the last two decades [2]. No doubt this difficult to eliminate scarcity of donor hearts has strengthened the role of mechanical circulatory support according to the ESC guidelines. The use of mechanical circulatory support while waiting for a heart transplant has been assigned to class I recommendations. However, this statement emphasizes in fact the highest clinical value of heart transplantation, which is worth waiting for despite the need for advanced mechanical support [1].

Apart from the donor shortage the biggest challenge for the transplant community is a high primary graft failure PGF) rate. PGF is estimated to cause over 40% of all deaths after HTX [3, 4].

Troponins are widely used biomarkers of myocardial injury of varying etiology. Theoretically they should be a reliable indicator of multifactorial heart transplant injury immediately after the operation. However, reports on the relationship between troponin levels over the first days after HTX and the postoperative course are few [5, 6].

Tab. I. Troponin I levels over first days after HTX (Trop0 – Day 0, Trop1 – Day 1, Trop2 – Day 2, Trop3 – Day 3) $p < 0.0001$ (Kruskal-Wallis test)

	Median	qr
Trop0	16.9	9.9
Trop1	17.1	11.2
Trop2	11.6	13
Trop3	7.6	8.1

Aim of the study

The purpose of the present study was to assess the relationship between troponin I levels measured over the first few days after HTX and the postoperative clinical course, including a 6-month follow-up.

Material and methods

The retrospective analysis included 54 patients (5 F, 49 M), age 12-62 years (median age 52.0, qr. 15.0) after heart transplantation.

The inclusion criteria in this study were as follows:

- availability of troponin I levels measured over the first days after HTX (from day zero to day 3); troponin I levels were measured using the one-step immunoenzymatic assay (SIEMENS, Germany, normal range from 0.1 ng/ml) (in case of more than one troponin I measurement over 24 hours the highest value was considered in the analysis);
- donor hearts procured using the same standard techniques and the same cardioplegic solution CELSIOR in a volume of 4 liters (heart procurement and graft protection have been described elsewhere) [7, 8];
- in order to avoid bias the assessment of the relationship between Intensive Care Unit (ICU) length of stay and duration of respiratory therapy and troponin I levels was performed in patients who survived > 6 months after HTX.

All patients operated on in the Department of Cardiovascular Surgery and Transplantology, Institute of Cardiology, Jagiellonian University College of Medicine at John Paul II Hospital in Krakow and meeting the inclusion criteria were included in the analysis (changes in the methodology and type of measured troponin were the most important factors limiting the size of the study group).

Statistical analysis

All statistical analyses were carried out using STATISTICA v.8. The Shapiro-Wilk test for normality was used in the study. The measurement data which did *not* meet *normal* distribution *were* expressed by the *median* and *quartile range* (qr). The following tests were used if appropriate:

- Spearman *r* correlation,
- Mann-Whitney U-test,
- Kruskal-Wallis test.

Results

Over several consecutive days after HTX troponin I levels were elevated, reaching 7.6 (median) (minimum) at day 3 (Trop3) and 17.1 (median) (maximum) at day 1 (Trop1), $p < 0.0001$ (Kruskal-Wallis test) (Tab. I).

There was a positive correlation between respiratory therapy duration (median 2 days; qr 1.0) and troponin I levels over several consecutive days after HTX. However, the relationship was significant only at day 2 after HTX (Trop2)

Tab. II. Relationship between troponin I levels measured over first days after HTX and respiratory therapy duration (Trop0 – Day 0, Trop1 – Day 1, Trop2 – Day 2, Trop3 – Day 3)

	Duration of respiratory therapy	
	R	*p*
Trop0	0.19	0.22
Trop1	0.18	0.26
Trop2	**0.46**	**0.003***
Trop3	0.31	0.06

**Statistical significance (Spearman r correlation).*

Tab. III. Relationship between troponin I levels measured over first days after HTX and Intensive Care Unit (ICU) length of stay (Trop0 – Day 0, Trop1 – Day 1, Trop2 – Day 2, Trop3 – Day 3)

	ICU length of stay	
	R	*p*
Trop0	0.26	0.10
Trop1	**0.33**	**0.03***
Trop2	**0.40**	**0.01***
Trop3	**0.39**	**0.02***

**Statistical significance (Spearman r correlation).*

(Spearman r correlation) (Tab. II). There was also a positive correlation between ICU length of stay (median 7 days; qr 3.0) and troponin I values. The relationship was significant at day 1, day 2 and day 3 after HTX (Trop1, Trop2, Trop3) (Spearman r correlation) (Tab. III). Troponin I values measured over several consecutive days after HTX did not significantly affect 30-day survival (7/54 patients died) (p = 0.06; p = 0.2; p = 0.21; p = 0.14, respectively). There was however a significant relationship (positive correlation) between troponin I values at day 0, day 2 and day 3 after HTX (Trop0, Trop2, Trop3) and > 6-month survival after HTX (10/54 patients died) (Mann-Whitney U test) (Tab. IV).

Tab. IV. Relationship between troponin I levels measured over first days after HTX and survival > 6 months (Trop0 – Day 0, Trop1 – Day 1, Trop2 – Day 2, Trop3 – Day 3)

	Survival > 6 months	
	U	*p*
Trop0	**90.0**	**0.04***
Trop1	140.0	0.10
Trop2	**93.0**	**0.03***
Trop3	**86.0**	**0.02***

**Statistical significance (Mann-Whitney U test).*

Discussion

The donor shortage which limits heart transplants is difficult to eliminate. In 2005 in Poland there were 95 heart transplants in the year, and only 61, 71, 79 and 80 between 2008 and 2011 [9]. This fact automatically forced qualification for HTX of externally sick patients. For this reason optimization of early and long-term outcomes for patients with HTX should be a priority. HTX outcomes have been assessed in single and multicenter studies addressing mainly the influence of common complications on survival and quality of life after HTX as well as exploring the most frequent factors limiting the expected medical outcomes in transplant recipients such as primary graft failure, infection, acute and chronic rejection or complications of immunosuppression [10, 11].

Troponins are markers of myocardial injury widely used in cardiology and cardiac surgery. Troponin levels are routinely measured at our institution after cardiac surgery. A heart transplantation is associated with many factors that can cause damage to the myocardium; therefore troponin values at different time points after HTX are usually markedly elevated [7, 8, 12]. Troponins, similar to CK-MB isoenzyme, are also almost always determined prior to heart procurement. However, the role of their elevated levels and most importantly their real effect on "heart transplant capacity" is not yet well understood. Some investigators advise against abstaining from heart procurement in case of high troponin levels if an echocardiogram reveals good cardiac function [13, 14]. There are only a few reports defining the effects of high troponin levels on the clinical course in patients after HTX. In our previous study there was no significant effect of troponin I levels measured over the first few days after HTX on myocardial ischemic injury (biopsy specimen obtained at 10 days after HTX) [15]. In 2000 Labarrere *et al.* assessed 110 patients undergoing heart transplantation. They found a significantly increased risk of coronary artery disease (vasculopathy) and graft failure in patients with elevated troponin I levels for one year after HTX [16].

In the present study troponin I levels over the first days after HTX had a significant influence on intensive care unit length of stay and respiratory therapy duration. Furthermore, troponin I levels measured at day 0, day 2 and day 3 after HTX correlated with > 6-month survival (the higher the level of troponin I the higher the risk of death). Given the paucity of the relevant literature results it is not possible to carry out comparative analyses. However, Amarelli *et al.* recently reported on a study in which the troponin I values at day 1 after HTX significantly affected the risk of primary graft failure [5].

The small sample size does not allow any definitive conclusions. Nevertheless, the present study reveals statistically proven effects of troponin I levels measured over the first days after HTX on the clinical course and survival.

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